Informed Consent in *Privacy and Progress in Whole Genome Sequencing*

Contents

I. Introduction

In *Privacy and Progress in Whole Genome Sequencing* (*Privacy and Progress*), the Presidential Commission for the Study of Bioethical Issues (Bioethics Commission) addressed the potential medical benefits and important privacy risks associated with the emerging technologies around whole genome sequencing and the large-scale collection of genomic data:

> Large-scale collections of genomic data raise serious concerns for the individuals participating. One of the greatest of these concerns centers around privacy: whether and how personal, sensitive, or intimate knowledge and use of that knowledge about an individual can be limited or restricted (by means that include guarantees of confidentiality, anonymity, or secure data protection). Because whole genome sequence data provide important insights into the medical and related life prospects of individuals as well as their relatives—who most likely did not consent to the sequencing procedure—these privacy concerns extend beyond those of the individual participating in whole genome sequencing. These concerns are compounded by the fact that whole genome sequence data gathered now may

> well reveal important information, entirely unanticipated and unplanned for, only after years of scientific progress.[1]

The Bioethics Commission issued the report proactively as an analysis of potential future challenges likely to arise as whole genome sequencing becomes more affordable and widely accessible in clinical and research settings as well as directly to consumers. The Bioethics Commission points out:

> Not unique to whole genome sequencing, a well-developed, understandable, informed consent process is essential to ethical clinical care and research. To educate patients and participants thoroughly about the potential risks associated with whole genome sequencing, the consent process must include information about what whole genome sequencing is; how data will be analyzed, stored, and shared; the types of results the patient and participant can expect to receive, if relevant; and the likelihood that the implications of some of these results might currently be unknown, but could be discovered in the future. Respect for persons requires obtaining fully informed consent at the outset of diagnostic testing or research.[2]

II. Learning Objectives

Students should be able to:

1. Describe current informed consent procedures for whole genome sequencing.
2. Describe recommendations for improving informed consent procedures for whole genome sequencing.
3. Identify aspects of whole genome sequencing that raise distinct ethical and practical issues with regard to informed consent.
4. Describe how data sharing relates to and affects the informed consent process.
5. Describe how privacy relates to and affects the informed consent process.

[1] Presidential Commission for the Study of Bioethical Issues (PCSBI). (2012, October). *Privacy and Progress in Whole Genome Sequencing*. Washington, DC: PCSBI, p 2.
[2] PCSBI, (2012, October), op cit, pp. 7-8.

III. Background

A. Biological Samples and Genomic Data

When biological samples are taken in the clinical (medical treatment) or research context, they—or the genetic or genomic data they generate—can be stored along with personal or medical information in biobanks for future research, warranting additional consideration of the informed consent process. When this happens, information and samples can be de-identified (i.e., the removal of traditional personal identifiers through use of a code) or anonymized (i.e., the permanent removal of all links between the sample or data and the person from whom it came) so that they cannot be re-connected to the person from whom they originated. Importantly, in de-identified samples, the "key" linking the individual to the sample might be maintained in a secure location to allow for reidentification should the need arise, whereas later reidentification is not possible when samples are anonymized. The intent to store biological samples or data for future research and plans for either de-identifying or anonymizing data or samples should be clearly indicated to research participants during in the informed consent process.

When samples or data are to be stored for possible future use, several approaches to the informed consent process can be considered.[3] One consent model requires participants to "opt in" to current or future research, giving explicit permission for the use of their samples or data. In another model, participants must actively "opt out" of research if they do not want their biological samples or data stored and used in current or future research. Alternatively, "broad consent" processes allow for current and future access and use of samples or data for research without necessarily specifying what the focus of such studies might be. Finally, "tiered" consent involves participants consenting to certain types of future research but not others. In considering the differences between these informed consent models, the Bioethics Commission points out:

> [a]s long as consent processes are equivalently effective in informing individuals about what they are consenting to, and as long as they do not unduly shape or undermine individuals' ability to make genuinely voluntary choices, there is no philosophical or ethical imperative to use one kind of consent process over another.[4]

B. Incidental Findings

In *Privacy and Progress*, the Bioethics Commission adopted a context- and modality-specific definition of incidental findings as "information gleaned from whole genome sequencing research or clinical practice that was not its intended or expected object."[5] They are not intended results of the procedure or study, and as a consequence, can present a host of ethical questions

[3] Bathe, O.F., and A.L. McGuire. (2009). The ethical use of existing samples for genome research. *Genetics in Medicine*, 11(10), 712-715.
[4] PCSBI, (2012, October), op cit, p. 92.
[5] PCSBI, (2012, October), op cit, p. 8.

such as when it is acceptable or necessary to report those findings to a research participant. Because whole genome sequencing can reveal a vast array of potentially clinically important information, these concerns are heightened in this context.

C. Bioethics Commission Recommendations

Of the 12 recommendations the Bioethics Commission issued in *Privacy and Progress*, four specifically address informed consent in the context of whole genome sequencing.

> **Recommendation 3.1**
>
> **Researchers and clinicians should evaluate and adopt robust and workable consent processes that allow research participants, patients, and others to understand who has access to their whole genome sequences and other data generated in the course of research, clinical, or commercial sequencing, and to know how these data might be used in the future. Consent processes should ascertain participant or patient preferences at the time the samples are obtained.[6]**
>
> **Recommendation 3.2**
>
> **The federal Office for Human Research Protections or a designated central organizing federal agency should establish clear and consistent guidelines for informed consent forms for research conducted by those under the purview of the Common Rule that involves whole genome sequencing. Informed consent forms should: 1) briefly describe whole genome sequencing and analysis; 2) state how the data will be used in the present study, and state, to the extent feasible, how the data might be used in the future; 3) explain the extent to which the individual will have control over future data use; 4) define benefits, potential risks, and state that there might be unknown future risks; and 5) state what data and information, if any, might be returned to the individual.[7]**
>
> **Recommendation 3.3**
>
> **Researchers, clinicians, and commercial whole genome sequencing entities must make individuals aware that incidental findings are likely to be discovered in the course of whole genome sequencing. The consent process should convey whether these findings will be communicated, the scope of communicated findings, and to whom the findings will be communicated.[8]**

[6] PCSBI, (2012, October), op cit, p. 91.
[7] PCSBI, (2012, October), op cit, p. 94.
[8] PCSBI, (2012, October), op cit, p. 98.

Recommendation 3.4

Funders of whole genome sequencing research should support studies to evaluate proposed frameworks for offering return of incidental findings and other research results derived from whole genome sequencing. Funders should also investigate the related preferences and expectations of the individuals contributing samples and data to genomic research and undergoing whole genome sequencing in clinical care, research, or commercial contexts.[9]

Individuals undergoing whole genome sequencing in research, clinical, and commercial contexts must be provided with sufficient information in informed consent documents to understand what incidental findings are, and to know if they will or will not be notified of incidental findings discovered as a result of whole genome sequencing.[10]

IV. Reading

For the purposes of discussion, students should download and read the following Bioethics Commission materials (reports are available for download on the Bioethics Commission's website at www.bioethics.gov under "Projects"):

Privacy and Progress in Whole Genome Sequencing, pp. 87-99 ("Consent").

V. Discussion Questions

The following questions are based on the information provided above and through the indicated reading and are intended to reinforce important aspects of informed consent highlighted in *Privacy and Progress*. Important points are noted with each question to help the instructor guide a group discussion. The "Additional Resources" section will be helpful in answering these questions.

1. **Why is it important for researchers to ascertain participant or patient preferences regarding future research use of whole genome sequencing data at the time that samples or data are obtained?**

   Starting points for discussion:

   a. If future research use of genomic information is possible because of storage and maintenance of biological samples and/or genomic data, then this possibility should be described during the informed consent process so that participants or

[9] Ibid.
[10] PCSBI, (2012, October), op cit, p. 9.

patients can make informed decisions regarding their participation in current or future research.

b. Re-consent, or consent for secondary research with pre-existing samples, can be costly and difficult to conduct. Re-consent is also difficult and sometimes impossible if samples have been anonymized or de-identified.

2. Ascertaining patient preferences regarding future use of biological samples or genomic data can employ a variety of approaches. What are the advantages and disadvantages of the various approaches to informed consent?

Starting points for discussion:

a. A range of informed consent mechanisms can be used to inform individuals about future use of data or samples and ascertain their preferences. There are advantages and disadvantages to each, including (but not limited to):

b. Opt-in
   i. *Pro*: Clearly respectful of autonomous decision making.
   ii. *Con*: Requiring explicit consent might limit or slow the progress of research since it tends to generate lower enrollment than does opt-out consent (in which participation is the default).
   iii. Opt-in consent is the most appropriate form of informed consent when samples or data remain identified or readily identifiable.

c. Opt-out
   i. *Pro*: Rates of participation are typically higher than in opt-in consent research since the default position is participation. This approach supports more rapid compiling of data and enables the progress of research using those data.
   ii. *Con*: Might be considered by some to be deceptive, depending on how the option is presented (e.g., if the choice is in the "fine print" of a consent form). Note that an opt-out consent process is ethical as long as the potential participant is fully informed of the ability to opt out of the research.

d. Broad consent
   i. *Pro*: Researchers have more freedom to use and share specimens and data for advancing research that they did not envision at the time of data or specimen collection. Additionally, participants have the option to participate maximally in future studies without being re-contacted for additional consent, which some consider to be cumbersome.

ii. *Con*: Participants are unaware of the types of research that might use their samples or data. This might not be considered a "con" for some participants. Some commentators have argued that if participants do not know the specifics of the planned research, their consent cannot be considered to be "fully informed" and therefore, does not fully respect the autonomy of participants. There is ongoing debate about this issue.

e. Tiered consent
   i. *Pro*: Provides participants with a number of choices.
   ii. *Con*: Might complicate the informed consent process. Researchers are responsible for keeping track of what research might be conducted with specific samples, which requires an extensive tracking system.

3. The unauthorized disclosure of genetic information is considered a research risk. Identify three aspects related to genetic information that, if disclosed, could be considered risks to an individual. How do these risks compare to the risks of unauthorized disclosure of other personal non-genomic information (e.g., social security numbers or credit card information)?

Starting points for discussion:

a. Answers might include: Non-paternity, susceptibility to diseases for which there is no current effective therapy, susceptibility to unfavorable social traits, and likelihood of childhood or late-onset conditions (disclosure of which may have professional, personal, and familial repercussions).

b. The disclosure of genomic information could have implications for biological relatives and future generations. Disclosures of other types of information (e.g., social security numbers or credit card information) are more likely to affect only the person to whom they belong.

4. Why is it important for participants to be aware of how incidental findings will be treated within the research context in which they are involved?

Starting points for discussion:

a. Participants should be fully informed about the potential to discover unexpected information about their health. Being informed provides participants with the opportunity to decide whether they want to receive such information if it is discovered.

b. These findings might or might not have clinical significance and also might or might not be actionable.

c. Participants should be fully informed regarding whether these findings will be reported to them, if detected. Otherwise, they might assume that a researcher's silence indicates that no health concerns were detected and as a result, the participant might be less diligent about pursuing specific screening measures, for example, mammograms, colonoscopies, or routine blood tests.

5. What are the advantages or disadvantages of having a designated federal central organizing agency develop guidelines for informed consent in whole genome sequencing?

Starting points for discussion:

a. *Advantage*: Uniform guidance will shape the way informed consent is handled in whole genome sequencing research and establish consistent guidance for protecting patients and participants.

b. *Disadvantage*: Less flexibility in state regulation (although states would be free to implement additional, higher-level protections).

6. Who might have access to participants' data after they are collected? In what topics might future researchers be interested? Would research participants likely anticipate this type of access?

Starting points for discussion:

a. Other researchers within the same institution or outside of the institution might have access to shared data in the future.

b. Data might or might not be anonymized or de-identified when they are deposited in a biobank or otherwise stored for later use. Data could be shared with no one or with a large number of researchers.

c. Future researchers might be interested in a sample because of, for example, a participant's race, age, or medical history.

d. Many participants likely would not anticipate this type of access or the variety of possible uses unless they were informed.

7. How much information should participants have about future research uses of genomic data or samples? Why?

Starting points for discussion:

a. This answer might differ with students' points of view. Some might argue that participants should only be informed of future uses if their samples or data are not de-identified and anonymized (i.e., identifiable), others might assert that there is always a need to inform participants of future uses, regardless of identifiability. Additionally, some might argue that future studies must be specified, others will argue that broad classes of studies (e.g., genetic studies or heart-health studies) should be specified, and still others would argue for more specific information about potential projects (e.g., a study sponsored by a research hospital regarding diabetes in 18-25 year olds).

8. How much control should participants have over future research uses of their genomic data or specimens? Why?

Starting points for discussion:

a. This answer might differ with students' points of view. Some might argue that participants should have total control over future uses, that they should be informed of possible future uses at the outset of a study, and that they should be able to select which future studies to participate in. Some might also argue that re-contact should be sought and re-consent obtained from participants when their samples are re-used. Others might say that this level of control is not only impractical and costly but also unnecessary given the minimal risks of the research.

VI. Problem-Based Learning

Scenario A. *The BioVU database at Vanderbilt University "has collected DNA samples from almost 150,000 individuals…Unless patients check a box indicating that they do not want their DNA in the BioVU database, their samples are included."*[11]

1. What type of informed consent is this?

Starting points for discussion:

a. BioVU employs an opt-out consent process. Some of the advantages and disadvantages of an opt-out consent process are discussed in Discussion Question 2, above.

[11] PCSBI, (2012, October), op cit, p. 93, regarding secondary researchers.

2. How does the management of this database reconcile individual privacy and scientific progress?

Starting points for discussion:

a. In addition to the BioVU website, the following article provides both detailed and descriptive information about the BioVU opt-out consent process:

> Pulley, J., et al. (2010). Principles of human subjects protections applied in an opt-out de-identified biobank. *Clinical Translational Science*, 3(1), 42-48.

What are the privacy concerns associated with the types of data being collected?

b. The de-identification system employed by BioVU entails the use of an electronic medical record system that removes personal identifiers from all data allowing data to be linked to a sample without identifying the individual from which the sample originated.

c. By enabling a mechanism to collect large numbers of de-identified biological samples and their corresponding data, BioVU generates large pools of information that can be accessed for genomic research.

Scenario B. *A researcher is reviewing an informed consent form with a prospective participant for a study involving a genetic test for a gene related to color-blindness. The participant is eager to engage in research on color-blindness but is alarmed at a line in the consent form that states that the de-identified samples may be used by other researchers for unspecified future research.*

1. What does this line of the consent form mean?

Starting points for discussion:

a. The researcher may share de-identified samples from this research project with other researchers for work on other projects, which could reveal more than information about color-blindness.

b. De-identification refers to the process of removing identifiable information, or information that can be used by the investigator to link an individual to his or her sample.

2. What might you, as an investigator, add to this section of the consent form to make it easier for the participant to understand?

Starting points for discussion:

a. That any samples shared will be de-identified, and what that means.

b. Whether the participant will be notified about future research conducted or the outcome of that research.

c. Whether the participant will be contacted to re-consent to future research.

d. The ability to opt-out of participation in future research.

e. Examples of other types of research that might be conducted now or in the future.

Scenario C. *A family decides to purchase a "direct-to-consumer" genetic testing kit to further their family genealogy research hobby. As part of the ordering process, each member of the family has received a series of forms to sign regarding the use of the data gleaned from the samples they will share with the genetic testing company. One of the family members notices that the form says that de-identified data will go into a databank that will be "shared with researchers around the globe."*

1. **What concerns do you think this family might have about sharing their data and how would this influence their decision to consent to such sharing?**

   Starting points for discussion:

   a. *Re-identification of data*: Will the family's medical or other information remain anonymous?

   b. *Sharing of personal information*: Will the family's private health information be accessible to other parties?

VII. Exercises

Exercise A. *Find an example of an informed consent document for whole genome sequencing. Some research projects make their informed consent documents available on the Internet. Additionally, the following article provides useful information:*

> Rotimi, C.N., and P.A. Marshall. (2010). Tailoring the process of informed consent in genetic and genomic research. *Genome Medicine,* 2(3), 20.

1. **How much information is the patient/participant given? List information regarding: purpose of study, who is in charge of the study, what samples will be taken, how samples will be used, future research, and handling of incidental findings.**

2. **If you were a potential participant, in what areas might you want more information?**

3. **What parts of the form are clear? Which are confusing?**

Exercise B. *Design an informed consent document for a study about Alzheimer's disease in which you enroll patients at major hospitals around the world. Consult international research ethics guidelines, some of which are addressed in the Informed Consent: Background module and others can be found through an online search.*

1. **Note special elements of the informed consent process relating to patients who might have diminished mental capacity and who therefore might have caregivers attending to their medical care and research authorizations.**

2. **Note special elements of the informed consent process related to enrolling patients at multiple sites in different countries.**

    Use 45 C.F.R. § 46.116 as a guide for important parts of the informed consent form. International research ethics guidelines such as the *Declaration of Helsinki* and the Nuremberg Code, among others, can be consulted.

VIII. Glossary of Terms

Biobank (biorepository): A stored collection of physical biological samples (e.g., blood or tissue); some biobanks also store associated data (e.g., medical information).

Whole genome sequencing: Determining the order of nucleotide bases—As, Ts, Gs, and Cs—in an individual's entire DNA sequence.

IX. Additional Resources

Bathe, O.F., and A.L. McGuire. (2009). The ethical use of existing samples for genome research. *Genetics in Medicine*, 11(10), 712-715.

McGuire, A.L., and L.M. Beskow. (2010). Informed consent in genomics and genetic research. *Annual Review of Genomics and Human Genetics*, 11, 361-381.

McGuire, A.L., et al. (2008). DNA data sharing: Research participants' perspectives. *Journal of Medical Genetics*, 10(1), 46-53.

Mello, M.M., and L.E. Wolf. (2010). The Havasupai Indian tribe case—Lessons for research involving stored biologic samples. *New England Journal of Medicine*, 363(3), 205.

Pulley, J., et al. (2010). Principles of human subjects protections applied in an opt-out de-identified biobank. *Clinical Translational Science*. 3(1), 42-48.

Rotimi, C.N., and P.A. Marshall. (2010). Tailoring the process of informed consent in genetic and genomic research. *Genome Medicine,* 2(3), 20.

Presidential Commission for the Study of Bioethical Issues. (2013, December). *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Contexts.* Washington, DC: PCSBI.

Singleton, P., and M. Wadsworth. (2006). Consent for the use of personal medical data in research. *British Medical Journal,* 333(7561), 255-258.

Terry, S.F., and P.F. Terry. (2001). A consumer perspective on informed consent and third party issues. *Journal of Continuing Education in the Health Professions,* 21(4), 256-264.

Valle-Mansilla, J.I., Ruiz-Canela, M., and D.P. Sulmasy. (2010). Patients' attitudes to informed consent for genomic research with donated samples. *Cancer Investigation*, 28(7), 726-734.